Intracavernous Injections in Spinal Cord Injured Men With Erectile Dysfunction, a Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Despite improvements in the care of patients after spinal cord injury (SCI), permanent impairment of locomotion, sensation, and autonomic function remains a major hurdle. After the acute stage of injury, recovering sexual function is a high priority.

Aim: To review the efficacy of intracavernous injections (ICIs) in men with SCI and to identify prognostic factors affecting the efficacy of ICIs in this population.

Methods: Systematic review of the literature was conducted using the PubMed-Medline, Embase, EBSCO, Web of Science, and Cochrane Library databases. The literature search was restricted to articles published in English, French, and Spanish up to November 2014 using the key words *alprostadil, papaverine, moxisylite, alpha-blocking agent, phentolamine, intracavernous injection, spinal cord injuries, paraplegia, quadriplegia,* and *erectile dysfunction.* Studies involving patients with SCI and erectile dysfunction treated with ICIs of alprostadil, papaverine, and α-blocking agents, including retrospective and prospective cohorts, population studies, and randomized controlled trials, were included.

Main Outcome Measure: Overall response rate to ICI for erectile dysfunction in patients with SCI.

Results: Of 283 studies identified, 23 involved 713 patients with SCI. ICIs resulted in successful erections in 88% of patients (n = 713, 95% CI = 83%−92%). Erections were obtained in 93% of patients (n = 101, 95% CI = 83%−99%) with the combination of papaverine and phentolamine, in 91% (n = 274, 95% CI = 78%−97%) with papaverine alone, and in 80% (n = 119, 95% CI = 64%−90%) with alprostadil. Type of injected drug, doses, level of injury (complete or incomplete), extent of injury, age, time since injury, and persistence or transience of erections were evaluated, but statistical analysis could not identify specific factors predictive of a response to ICI.

Conclusion: ICIs are an effective treatment of erectile dysfunction in men with SCI. No predictive factor for efficacy could be identified. Studies comparing the response to ICI in upper vs lower motor neuron lesions could improve our understanding of ICI failure.

Sex Med Rev 2016;4:257−269.

Key Words: Paraplegia; Quadriplegia; Erectile Dysfunction; Alprostadil; Papaverine

INTRODUCTION

Despite improvements in the care of patients after spinal cord injury (SCI), permanent impairment of locomotion, sensation, and autonomic function remains a major hurdle. Sexual and reproductive functions are of primary importance. After the acute stage of injury, recovering sexual function is the first priority for paraplegics and the second for quadriplegics.[1]

Erectile dysfunction (ED), defined as the inability to attain and maintain penile erection sufficient for satisfactory sexual performance,[2] is common in patients with SCI. In this pathologic context, ED of neurogenic origin depends on the level and extent of the lesion.[3] Reflexive erections triggered by peripheral stimulation, especially when applied to the penis or the peri-genital area, occur in patients with intact sacral conus medullaris and independent of supraspinal connections. Psychogenic erection triggered by stimuli processed by the brain

Received January 19, 2016. Accepted February 22, 2016.

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http://dx.doi.org/10.1016/j.sxmr.2016.02.005

(visual, auditory, or fantasy) is observed in patients with preserved and supraspinal connected sacral parasympathetic centers located in spinal segments S2 to S4 or, in case of injured or disconnected sacral segments, preserved spinal segments T12 to L2.[4,5] Overall, the exact impairment of erectile function depends on the type of SCI in terms of the completeness of the injury and its location within the spinal cord.[6] Although most men with SCI can have some type of erection (ie, psychogenic or reflexive), erectile responses often are not sufficiently predictable, rigid, or long-lasting enough for satisfactory sexual intercourse.[7–9] Oral phosphodiesterase type 5 inhibitors (PDE5is) are first-line treatment for patients with ED, whatever the etiology.[10] Based on multinational randomized placebo-controlled clinical trials in patients with SCI,[11–14] in the summary of indications and product characteristics, ED from SCI is actually mentioned for PDE5is sildenafil, vardenafil, and tadalafil. Patients with SCI not responding to PDEi might receive intracavernous injections (ICIs)[2] or a vacuum device. The first PDE5i, sildenafil, was launched in 1998, and the first reports about the pro-erectile effect of intracavernous delivery of papaverine and phentolamine were published in 1982 and 1983, respectively.[15,16] Commonly used single agents for ICI include prostaglandin E1 (PGE1; eg, alprostadil, papaverine, and moxisylite), an α-adrenoreceptor blocking agent (no longer available). PGE1, papaverine, vasoactive intestinal polypeptide, phentolamine, phenoxybenzamine (phentolamine and phenoxybenzamine are adrenoreceptor blocking agents), and chlorpromazine have been combined to treat ED.[16–18] The most frequently used combinations include papaverine plus phenoxybenzamine (bi-mix) and PGE1 (tri-mix). Men or their partners (especially for quadriplegics) must be taught how to inject the penis during dose titration in the physician's office. First, the material is presented: prefilled syringes or drug vials with syringes, including 28- to 30-gauge needles, and alcohol swabs. Second, patients are instructed to draw up the drugs aseptically for non-prefilled syringes. Third, patients are taught how to inject laterally into the left or right corpus cavernosum at a 90° angle to the penis, avoiding the urethra, dorsal penile nerve, and veins. After the injection, pressure to the injection site must be applied for 2 minutes. Erection usually occurs within a few minutes, independent of sexual stimulation. Thus, pharmacologically induced erections by ICIs differ from facilitated erections by PDE5i with mandatory sexual stimulation. After adequate training by an experienced physician, a program of home self-injection therapy can be initiated. The titration of the dose required to achieve a satisfactory erection remains unpredictable in patients with SCI and sometimes ICIs fail. Then, a vacuum device or, for the rare case of failure, penile implants, as third-line treatment, can be proposed. Predictive factors for the success of ICIs in patients with SCI have not been evaluated.

The objectives of this systematic review and meta-analysis were to assess (i) the efficacy of ICI and to determine the (ii) demographic and (iii) predictive factors of response to ICIs according to spinal cord lesion in patients with SCI.

METHODS

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.[19] We developed and followed a standard protocol of meta-analysis recorded on the PROSPERO database[20] (PROSPERO 2014:CRD42014009288).

Eligibility Criteria

Type of Participants

We reviewed studies reporting data about men with SCI and ED.

Type of Intervention

Studies were eligible if they involved the use of ICIs, whatever drug was used.

Types of Studies

All prospective and retrospective designs assessing response to ICI were eligible for this review: randomized controlled trials, non-randomized cohort studies, and cases series were included. The literature search was restricted to reports in English, French, and Spanish published up to November 2014.

Type of Outcome

Studies were retained if they reported the response to ICIs, defined as (i) a Schrameck grade of at least 4 to 5 (grade 1 = no erection, grade 2 = slight tumescence, grade 3 = full volume without rigidity, grade 4 = sufficient for sexual intercourse, grade 5 = full erection)[21] and/or (ii) rigidity allowing intromission and/or (iii) full erection and/or (iv) successful intercourse and/or (v) satisfactory erection suitable for sexual intercourse.

Search Strategy

Eligible studies were identified from the PubMed-Medline, Cochrane Library, Embase, EBSCO, and Web of Science databases. An initial search on Medline was carried out to refresh optimal search terms. The search terms retained were doubly checked before starting the main search of all the databases. A final search was undertaken using the reference lists of articles identified (including a previous meta-analysis). The initial Medical Subject Heading terms were *alprostadil* OR *papaverine* OR *intracavernous injection* OR *moxisylite* OR *phentolamine* AND *spinal cord injuries* OR *paraplegia* OR *quadriplegia* AND *erectile dysfunction*.

Studies Selection

Eligibility assessment was performed independently in a blinded standardized manner by two reviewers (L.C. and C.C.) and subsequently crosschecked. Disagreements were resolved by